

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1 - 25 (canceled).

26 (currently amended). The method of claim
[[25]] 161, wherein said sequence alteration is a
substitution of at least one base.

27 (currently amended). The method of claim
[[25]] 161, wherein said sequence alteration is a deletion
of at least one base.

28 (currently amended). The method of claim
[[25]] 161, wherein said alteration is an insertion of at
least one base.

29 - 32 (canceled).

33 (previously presented). The method of claim
[[32]] 161, wherein said chromosome is an artificial
chromosome.

34 (canceled).

35 (currently amended). The method of claim
[[25]] 161, wherein said cellular repair proteins are
purified.

36 (currently amended). The method of claim
[[25]] 161, wherein said cellular repair proteins are
present in a cell-free protein extract.

37 (currently amended). The method of claim
[[25]] 161, wherein said cellular repair proteins are
present within an intact cell.

38 (previously presented). The method of claim
37, wherein said cell is cultured *ex vivo*.

39 (canceled).

40 (currently amended). The method of claim
[[25]] 161, wherein said cellular repair proteins are of a
cell selected from the group consisting of: prokaryotic
cells and eukaryotic cells.

41 (previously presented). The method of claim
40, wherein said cell is a prokaryotic cell.

42 (previously presented). The method of claim
41, wherein said prokaryotic cell is a bacterial cell.

43 (previously presented). The method of claim
42, wherein said bacterial cell is an *E. coli* cell.

44 (previously presented). The method of claim 40, wherein said cell is a eukaryotic cell.

45 (previously presented). The method of claim 44, wherein said eukaryotic cell is a yeast cell, plant cell, human cell, or a mammalian cell.

46 (previously presented). The method of claim 45, wherein said eukaryotic cell is a yeast cell.

47 (previously presented). The method of claim 46, wherein said yeast cell is a *Saccharomyces cerevisiae*, *Ustilago maydis*, or *Candida albicans* cell.

48 (previously presented). The method of claim 45, wherein said eukaryotic cell is a plant cell.

49 (previously presented). The method of claim 45, wherein said eukaryotic cell is a human cell.

50 (previously presented). The method of claim 49, wherein said human cell is selected from the group consisting of liver cell, lung cell, colon cell, cervical cell, kidney cell, epithelial cell, cancer cell, and stem cell.

51 (previously presented). The method of claim 45, wherein said eukaryotic cell is from a mammal.

52 (previously presented). The method of claim 51, wherein said mammal is selected from the group consisting of: rodent, mouse, hamster, rat, and monkey.

53 (currently amended). The method of claim ~~[[25]]~~ 161, wherein said oligonucleotide is at least 25 nucleotides in length.

54 (currently amended). The method of claim ~~[[25]]~~ 161, wherein said oligonucleotide is no more than 74 nucleotides in length.

55 (canceled).

56 (currently amended). The method of claim ~~[[25]]~~ 161, wherein said first strand is the nontranscribed strand of the target nucleic acid.

57 (currently amended). The method of claim ~~[[25]]~~ 161, wherein the sequences of said deoxyribonucleotide domain and of the target nucleic acid first strand are mismatched at a single nucleotide.

58 (currently amended). The method of claim ~~[[25]]~~ 161, wherein the sequences of said deoxyribonucleotide domain and of its complement on the target nucleic acid first strand are mismatched at two or more nucleotides.

59 (currently amended). The method of claim [[25]] 161, wherein said at least one terminal modification is at least one 3' terminal LNA analogue.

60 (previously presented). The method of claim 59, wherein said oligonucleotide has no more than 3 LNA analogues at its 3' terminus.

61 (previously presented). The method of claim 59, wherein said oligonucleotide has at least one LNA at its 3' terminus and at least one LNA at its 5' terminus.

62 (previously presented). The method of claim 61, wherein said oligonucleotide has no more than 3 contiguous LNA at each of its 3' or 5' termini.

63 (currently amended). The method of claim [[25]] 161, wherein said at least one terminal modification is at least one 2'-O-methyl ribonucleotide analog at its 3' terminus.

64 (previously presented). The method of claim 63, wherein said oligonucleotide has no more than 4 contiguous 2'-O-methyl ribonucleotide analogs.

65 (previously presented). The method of claim 63, wherein said oligonucleotide has at least one 2'-O-methyl ribonucleotide analog at its 3' terminus and at least one 2'-O-methyl ribonucleotide analog at its 5' terminus.

66 (previously presented). The method of claim 65, wherein said oligonucleotide has no more than 4 contiguous 2'-O-methyl ribonucleotide analogs.

67 (currently amended). The method of claim [[25]] 161, wherein said at least one terminal modification comprises at least three terminal phosphorothioate linkages.

68 (previously presented). The method of claim 67, wherein said phosphorothioate linkages at said oligonucleotide's 3' terminus.

69 (previously presented). The method of claim 67, wherein said oligonucleotide comprises no more than 6 contiguous phosphorothioate linkages.

70 (currently amended). A method of targeted sequence alteration of a nucleic acid present within selectively enriched cells in vitro, cells in culture, or cell-free extracts, comprising:
combining the targeted nucleic acid in the presence of cellular repair proteins with a single-stranded nonhairpin oligonucleotide 17 - 121 nucleotides in length, said oligonucleotide having a domain of at least 8 contiguous deoxyribonucleotides,
wherein said oligonucleotide is fully complementary in sequence to the sequence of a first strand of the nucleic acid target, but for one or more mismatches as between the sequences of said deoxyribonucleotide domain and its complement on the target nucleic acid first strand,

each of said mismatches positioned at least 8 nucleotides from said oligonucleotide's 5' and 3' termini;

wherein said oligonucleotide has at least one terminal modification selected from the group consisting of: at least one terminal locked nucleic acid (LNA), at least one terminal 2'-O-Me base analog, and at least three terminal phosphorothioate linkages;

wherein said cultured or selectively enriched cells are not human embryonic stem cells, and

~~The method of claim 25~~, wherein said targeted nucleic acid is selected from the group of human genes consisting of: ADA, p53, beta-globin, RB, BRCA1, BRCA2, CFTR, CDKN2A, APC, Factor V, Factor VIII, Factor IX, hemoglobin alpha 1, hemoglobin alpha 2, MLH1, MSH2, MSH6, ApoE, LDL receptor, UGT1, APP, PSEN1, and PSEN2.

71 (previously presented). The method of claim 70, wherein said targeted nucleic acid is the human beta-globin gene.

72 (previously presented). The method of claim 71, wherein said human beta-globin gene is targeted in a human hematopoietic stem cell.

73 (currently amended). A method of targeted sequence alteration of a nucleic acid present within selectively enriched cells in vitro, cells in culture, or cell-free extracts, comprising:

combining the targeted nucleic acid in the presence of cellular repair proteins with a single-stranded

nonhairpin oligonucleotide 17 - 121 nucleotides in length,
said oligonucleotide having a domain of at least 8
contiguous deoxyribonucleotides,

wherein said oligonucleotide is fully
complementary in sequence to the sequence of a first strand
of the nucleic acid target, but for one or more mismatches
as between the sequences of said deoxyribonucleotide domain
and its complement on the target nucleic acid first strand,
each of said mismatches positioned at least 8 nucleotides
from said oligonucleotide's 5' and 3' termini;

wherein said oligonucleotide has at least one
terminal modification selected from the group consisting of:
at least one terminal locked nucleic acid (LNA), at least
one terminal 2'-O-Me base analog, and at least three
terminal phosphorothioate linkages;

wherein said cultured or selectively enriched
cells are not human embryonic stem cells, and

~~The method of claim 25,~~ wherein said
oligonucleotide ~~is 17 - 121 nucleotides in length and~~
includes the sequence of any one of SEQ ID NOs: 1 - 4340.

74 (previously presented). The method of claim
73, wherein said oligonucleotide has sequence identical to
any one of SEQ ID NOs: 1 - 4340.

75 (previously presented). A method of targeted
sequence alteration of a nucleic acid present within
selectively enriched cells *in vitro*, cells in culture, or
cell-free extracts, comprising:

combining the targeted nucleic acid in the presence of cellular repair proteins with a single-stranded nonhairpin oligonucleotide 17 - 121 nucleotides in length, said oligonucleotide having a domain of at least 8 contiguous deoxyribonucleotides,

wherein said oligonucleotide is fully complementary in sequence to the sequence of a first strand of the nucleic acid target, but for one or more mismatches as between the sequences of said deoxyribonucleotide domain and its complement on the target nucleic acid first strand, each of said mismatches positioned at least 8 nucleotides from said oligonucleotide's 5' and 3' termini;

wherein said oligonucleotide has at least one terminal modification, said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1 - 4340, and said cultured or selectively enriched cells are not human embryonic stem cells.

76 (previously presented). The method of claim 75, wherein said at least one terminal modification is selected from the group consisting of: at least one terminal locked nucleic acid (LNA), at least one terminal 2'-O-Me base analog, and at least three terminal phosphorothioate linkages.

77 (previously presented). The method of claim 75, wherein said target is chromosomal genomic DNA.

78 (previously presented). A method of targeted sequence alteration of a nucleic acid present within

selectively enriched hematopoietic stem cells *in vitro* or hematopoietic stem cells in culture, comprising:

combining the targeted nucleic acid in the presence of cellular repair proteins with a single-stranded nonhairpin oligonucleotide 17 - 121 nucleotides in length, said oligonucleotide having a domain of at least 8 contiguous deoxyribonucleotides,

wherein said oligonucleotide is fully complementary in sequence to the sequence of a first strand of the nucleic acid target, but for one or more mismatches as between the sequences of said deoxyribonucleotide domain and its complement on the target nucleic acid first strand, each of said mismatches positioned at least 8 nucleotides from said oligonucleotide's 5' and 3' termini; and

wherein said oligonucleotide has at least one terminal modification selected from the group consisting of: at least one terminal locked nucleic acid (LNA), at least one terminal 2'-O-Me base analog, and at least three terminal phosphorothioate linkages.

79 (new). The method of claim 70, wherein said targeted nucleic acid is the human ADA gene.

80 (new). The method of claim 79, wherein said ADA gene is targeted in a human hematopoietic stem cell.

81 (new). The method of claim 70, wherein said targeted nucleic acid is the human p53 gene.

82 (new). The method of claim 70, wherein said targeted nucleic acid is the human RB gene.

83 (new). The method of claim 70, wherein said targeted nucleic acid is the human BRCA1 gene.

84 (new). The method of claim 70, wherein said targeted nucleic acid is the human BRCA2 gene.

85 (new). The method of claim 70, wherein said targeted nucleic acid is the human CFTR gene.

86 (new). The method of claim 70, wherein said targeted nucleic acid is the human CDKN2A gene.

87 (new). The method of claim 70, wherein said targeted nucleic acid is the human APC gene.

88 (new). The method of claim 70, wherein said targeted nucleic acid is the human Factor V gene.

89 (new). The method of claim 70, wherein said targeted nucleic acid is the human Factor VIII gene.

90 (new). The method of claim 70, wherein said targeted nucleic acid is the human Factor IX gene.

91 (new). The method of claim 70, wherein said targeted nucleic acid is the human hemoglobin alpha 1 gene.

92 (new). The method of claim 91, wherein said hemoglobin gene is targeted in a human hematopoietic stem cell.

93 (new). The method of claim 70, wherein said targeted nucleic acid is the human hemoglobin alpha 2 gene.

94 (new). The method of claim 93, wherein said hemoglobin gene is targeted in a human hematopoietic stem cell.

95 (new). The method of claim 70, wherein said targeted nucleic acid is the human MLH1 gene.

96 (new). The method of claim 70, wherein said targeted nucleic acid is the human MSH2 gene.

97 (new). The method of claim 70, wherein said targeted nucleic acid is the human MSH6 gene.

98 (new). The method of claim 70, wherein said targeted nucleic acid is the human ApoE gene.

99 (new). The method of claim 70, wherein said targeted nucleic acid is the human LDL receptor.

100 (new). The method of claim 70, wherein said targeted nucleic acid is the human UGT1 gene.

101 (new). The method of claim 70, wherein said targeted nucleic acid is the human APP gene.

102 (new). The method of claim 70, wherein said targeted nucleic acid is the human PSEN1 gene.

103 (new). The method of claim 70, wherein said targeted nucleic acid is the human PSEN2 gene.

104 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1 - 160.

105 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 161 - 356.

106 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 357 - 500.

107 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 501 - 652.

108 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 653 - 1028.

109 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1029 - 1128.

110 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1129 - 1320.

111 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1321 - 1432.

112 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1433 - 1768.

113 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4340, 1769 - 1799.

114 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1800 - 2271.

115 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2272 - 2775.

116 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2776 - 2855.

117 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2856 - 2979.

118 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2980 - 3207.

119 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3208 - 3343.

120 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3344 - 3395.

121 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3396 - 3471.

122 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3472 - 3959.

123 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3960 - 4035.

124 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4036 - 4083.

125 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4084 - 4319.

126 (new). The method of claim 73, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4320 - 4339.

127 (new). The method of claim 73, wherein said oligonucleotide has sequence identical to any one of SEQ ID NOs: 1 - 4340.

128 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1 - 160.

129 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 161 - 356.

130 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 357 - 500.

131 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 501 - 652.

132 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 653 - 1028.

133 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1029 - 1128.

134 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1129 - 1320.

135 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1321 - 1432.

136 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1433 - 1768.

137 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4340, 1769 - 1799.

138 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1800 - 2271.

139 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2272 - 2775.

140 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2776 - 2855.

141 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2856 - 2979.

142 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2980 - 3207.

143 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3208 - 3343.

144 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3344 - 3395.

145 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3396 - 3471.

146 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3472 - 3959.

147 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 3960 - 4035.

148 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4036 - 4083.

149 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4084 - 4319.

150 (new). The method of claim 75, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 4320 - 4339.

151 (new). The method of claim 75, wherein said oligonucleotide has sequence identical to any one of SEQ ID NOs: 1 - 4340.

152 (new). The method of claim 78, wherein said oligonucleotide has at least three terminal phosphorothioate linkages.

153 (new). The method of claim 152, wherein said targeted nucleic acid is the human ADA gene.

154 (new). The method of claim 153, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 1 - 160.

155 (new). The method of claim 152, wherein said targeted nucleic acid is the human beta globin gene.

156 (new). The method of claim 155, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 357 - 500.

157 (new). The method of claim 152, wherein said targeted nucleic acid is the human hemoglobin alpha 1 gene.

158 (new). The method of claim 157, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2776 - 2855.

159 (new). The method of claim 152, wherein said targeted nucleic acid is the human hemoglobin alpha 2 gene.

160 (new). The method of claim 159, wherein said oligonucleotide includes the sequence of any one of SEQ ID NOs: 2856 - 2979.

161 (new). A method of targeted chromosomal sequence alteration, the method comprising:

introducing a sequence-altering oligonucleotide into a cell *in vitro*, wherein said sequence-altering oligonucleotide:

is a single-stranded nonhairpin
oligonucleotide 17 - 121 nucleotides in length;

has an unmodified DNA domain of at least 8 contiguous deoxyribonucleotides;

is fully complementary in sequence to a first strand of the cell's chromosomal DNA at a chromosomal target sequence, except for one or two mismatches positioned (i) within said oligonucleotide's unmodified DNA domain and (ii) at least 8 nucleotides from said oligonucleotide's 5' and 3' termini; and

has chemical modifications consisting essentially of at least one terminal locked nucleic acid (LNA), or at least one terminal 2'-O-Me base analog, or at least three terminal phosphorothioate linkages, or combinations thereof,

whereby said introduced oligonucleotide directs sequence alteration at said chromosomal target sequence by the cellular repair enzyme machinery.